NATIONAL TOXICOLOGY PROGRAM
Technical Report Series
No. 447

TOXICOLOGY AND CARCINOGENESIS STUDIES OF ACETONITRILE

(CAS NO. 75-05-8)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

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NTP TECHNICAL REPORT

ON THE

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CONTENTS

ABSTRACT

CH_3CN

ACETONITRILE

CAS No. 75-05-8

Chemical Formula: C_2H_3N Molecular Weight: 41.05

Synonyms: Cyanomethane, ethanenitrile, ethyl nitrile, methanecarbonitrile, methyl cyanide, nitrile of acetic acid

Acetonitrile is used primarily as a solvent in extractive distillation and crystallization of pharmaceutical and agricultural products and as a catalyst in chemical reactions. It was nominated for testing by the National Cancer Institute due to its presence in drinking water supplies and the environment, due to lack of information on the carcinogenicity of alkyl cyanides, and because of widespread worker exposure. Male and female F344/N rats and B6C3F$_1$ mice were exposed to acetonitrile (at least 99% pure) by inhalation for 13 weeks or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*, cultured Chinese hamster ovary cells, and peripheral blood of B6C3F$_1$ mice exposed to acetonitrile for 13 weeks.

13-WEEK STUDY IN RATS

Groups of 10 male and 10 female F344/N rats were exposed to 0, 100, 200, 400, 800, or 1,600 ppm (equivalent to 0, 168, 335, 670, 1,340, or 2,681 mg/m^3) acetonitrile by inhalation for 6 hours per day, 5 days per week for 13 weeks. Six male and three female rats that received 1,600 ppm and one male that received 800 ppm died during the study. At exposure concentrations up to and including 800 ppm, the final mean body weights and body weight gains were generally similar to those of the controls. At 1,600 ppm, body weight gain was lower and the final mean body weights of both males and females were significantly lower than those of the controls. Hypoactivity and ruffled fur were observed during the first week of the study in males receiving 800 ppm and males and females receiving 1,600 ppm. Additional clinical findings in 1,600 ppm males that died during week 1 were ataxia, abnormal posture, and clonic convulsions. Clinical pathology findings included nonresponsive, normocytic, normochromic anemia in 1,600 ppm males and females and in 800 ppm females, and decreased triiodothyronine (T_3) concentrations in 1,600 ppm females. Absolute and relative thymus weights were significantly lower than those of the controls in the 800 and 1,600 ppm males and females. Females exposed to 1,600 ppm had significantly greater absolute and relative heart, kidney, and liver weights than those of the controls. There were no clear exposure-related histopathologic effects, although pulmonary congestion and edema and hemorrhage in the lung and brain were seen in some rats that died early. These lesions are consistent with cyanide-induced anoxia.

13-Week Study in Mice

Groups of 10 male and 10 female B6C3F$_1$ mice were exposed to 0, 100, 200, 400, 800, or 1,600 ppm (equivalent to 0, 168, 335, 670, 1,340, or 2,681 mg/m^3) acetonitrile by inhalation for 6 hours per day, 5 days per week for 13 weeks. All mice exposed to 1,600 ppm died during the first 3 weeks of the study. In addition, one 400 ppm female and one male and four females from the 800 ppm groups also died before the end of the study. Body weight gains were similar to those of controls for all surviving groups of mice except the 800 ppm males, for which the final mean body weight was slightly lower than that of the controls. Clinical findings observed during the first week in 800 and 1,600 ppm mice were hypoactivity and a hunched, rigid posture. In males that received 200 ppm and above, absolute liver weights were greater than that of the controls and relative liver weights were greater in all exposed groups. In 800 ppm females, the absolute liver weight was greater than that of the controls and relative liver weights of females that received 400 ppm and above were greater than that of the controls. Lesions clearly associated with acetonitrile exposure were observed in the stomach, predominantly the forestomach, of males that received 400 ppm and above and of females that received 200 ppm and above. Histologically, these focal or multifocal pale to dark raised lesions consisted of areas of focal epithelial hyperplasia and ulceration, sometimes associated with hemosiderin deposition. An increased incidence of cytoplasmic vacuolation occurred in the liver of males and females exposed to 400 or 800 ppm. A lack of fatty degenerative change was observed in the X-zone of the adrenal cortex of 800 and 1,600 ppm female mice.

2-Year Study in Rats

The doses selected for the 2-year study of acetonitrile were based on reduced survival of 800 ppm males and 1,600 ppm males and females in the 13-week study. Groups of up to 56 male and 56 female rats were exposed to 0, 100, 200, or 400 ppm (equivalent to 0, 168, 335, or 670 mg/m^3) acetonitrile by inhalation for 6 hours per day, 5 days per week for 2 years. Eight male and eight female rats from each exposure group were evaluated at 15 months for histopathology and hematology parameters.

Survival, Body Weights, Clinical Findings, and Hematology

Two-year survival, mean body weights, organ weights, behavior, general health, and appearance of exposed male and female rats were similar to those of the controls. The hematologic effects observed were minor and of no biological significance.

Pathology Findings

The incidences of hepatocellular adenoma (3/48), hepatocellular carcinoma (3/48), and hepatocellular adenoma or carcinoma (combined; 5/48) were greater in male rats exposed to 400 ppm than in the controls (one carcinoma). The incidences of hepatocellular adenoma and hepatocellular carcinoma were within the range of historical controls. However, the incidence of hepatocellular adenoma or carcinoma (combined) slightly exceeded the range of historical controls (2%-8%). In addition, the incidences of basophilic, eosinophilic, and mixed cell foci in 400 ppm males were marginally greater than in controls, suggesting hepatotoxicity of acetonitrile. There were no exposure-related liver lesions in female rats.

2-Year Study in Mice

The exposure concentrations selected for the 2-year study were based on reduced survival and gross and histopathologic lesions in 400, 800, and 1,600 ppm groups of male and female mice in the 13-week study. Groups of 60 male and 60 female mice were exposed to 0, 50, 100, or 200 ppm (equivalent to 0, 84, 168, or 335 mg/m^3) acetonitrile by inhalation for 6 hours per day, 5 days per week for 2 years. Ten male and 10 female mice from each exposure group were evaluated at 15 months for histopathology.

Survival, Body Weights, and Clinical Findings

Two-year survival of exposed male and female mice was similar to that of the controls, except that the survival of male mice in the 200 ppm group was significantly greater than that of the controls. Mean body weights and organ weights of exposed groups of male and female mice were similar to those of the controls, and no clinical observations in any group were clearly related to acetonitrile exposure.

Pathology Findings

There were no increases in the incidences of neoplasms that were considered related to acetonitrile exposure in mice. The incidence of squamous hyperplasia of the epithelium of the forestomach was significantly increased at 15 months in 200 ppm females. At 2 years, the increased incidence of this lesion was dose related in all exposed groups of males and females.

GENETIC TOXICOLOGY

Acetonitrile was not mutagenic in *Salmonella typhimurium* strain TA97, TA98, TA100, TA1535, or TA1537, with or without S9 metabolic activation. In cultured Chinese hamster ovary cells, acetonitrile produced a weakly positive response in the sister chromatid exchange test without, but not with, S9. A small increase in chromosomal aberrations was observed in cultured Chinese hamster ovary cells treated with acetonitrile in the presence, but not in the absence, of S9. A significant increase in micronucleated normochromatic erythrocytes was observed in peripheral blood samples from male mice treated with acetonitrile for 13 weeks; the frequency of micronucleated erythrocytes in female mice was not affected by exposure to acetonitrile.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *equivocal evidence of carcinogenic activity** of acetonitrile in male F344/N rats based on marginally increased incidences of hepatocellular adenoma and carcinoma. There was *no evidence of carcinogenic activity* of acetonitrile in female F344/N rats exposed to 100, 200, or 400 ppm. There was *no evidence of carcinogenic activity* of acetonitrile in male or female $B6C3F_1$ mice exposed to 50, 100, or 200 ppm.

Exposure to acetonitrile by inhalation resulted in increased incidences of hepatic basophilic foci in male rats and of squamous hyperplasia of the forestomach in male and female mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Acetonitrile

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 100, 200, or 400 ppm by inhalation (equivalent to 0, 168, 335, or 670 mg/m^3)	0, 100, 200, or 400 ppm by inhalation (equivalent to 0, 168, 335, or 670 mg/m^3)	0, 50, 100, or 200 ppm by inhalation (equivalent to 0, 84, 168, or 335 mg/m^3)	0, 50, 100, or 200 ppm by inhalation (equivalent to 0, 84, 168, or 335 mg/m^3)
Body weights	Exposed groups similar to controls	Exposed groups similar to controls	Exposed groups similar to controls	Exposed groups similar to controls
2-Year survival rates	11/48, 13/47, 9/48, 17/48	23/48, 21/48, 26/48, 29/48	32/50, 32/50, 32/50, 43/50	28/50, 33/50, 29/50, 32/50
Nonneoplastic effects	Liver: basophilic focus (15/48, 22/47, 25/48, 31/48)	None	Forestomach: squamous hyperplasia (3/49, 3/50, 6/48, 12/50)	Forestomach: squamous hyperplasia (2/49, 7/50, 9/50, 19/48)
Neoplastic effects	None	None	None	None
Uncertain findings	Liver: hepatocellular adenoma (0/48, 1/47, 1/48, 3/48); hepatocellular carcinoma (1/48, 0/47, 0/48, 3/48); hepatocellular adenoma or carcinoma (combined) (1/48, 1/47, 1/48, 5/48)	None	None	None
Level of evidence of carcinogenic activity	Equivocal evidence	No evidence	No evidence	No evidence

Genetic toxicology

Salmonella typhimurium gene mutations:	Negative with and without S9 in strains TA97, TA98, TA100, TA1535, and TA1537
Sister chromatid exchanges	
Cultured Chinese hamster ovary cells *in vitro*:	Weakly positive without S9; negative with S9
Chromosomal aberrations	
Cultured Chinese hamster ovary cells *in vitro*:	Negative without S9; equivocal with S9
Micronucleated erythrocytes	
Mouse peripheral blood *in vivo*:	Negative in female mice; positive in male mice

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on acetonitrile on June 21, 1994, are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On June 21, 1994, the draft Technical Report on the toxicology and carcinogenesis studies of acetonitrile received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.R. Bucher, NIEHS, introduced the toxicology and carcinogenesis studies of acetonitrile by discussing the uses of the chemical and rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on possible chemical-related neoplastic lesions in male rats and nonneoplastic lesions in male and female mice. The proposed conclusions for the studies were *equivocal evidence of carcinogenic activity* in male F344/N rats, *no evidence of carcinogenic activity* in female F344/N rats, and *no evidence of carcinogenic activity* in male or female B6C3F$_1$ mice.

Dr. Taylor, a principal reviewer, agreed with the proposed conclusions. He suggested that a sentence be added to the conclusions that in the 2-year studies in male rats there might be some hepatotoxic effects based upon the findings of basophilic, eosinophilic, and mixed cell foci, and Dr. Bucher agreed. Dr. Taylor noted the statement that tobacco smoke contains acetonitrile and wondered if there was literature that could be cited with data quantifying the levels of acetonitrile in cigarette smoke.

Dr. Klaassen, the second principal reviewer, agreed with the proposed conclusions. He thought the highest exposure concentration of acetonitrile in the 2-year studies should have been higher in rats, perhaps 800 ppm.

Dr. Karol, the third principal reviewer, agreed with the proposed conclusions. She concurred with Dr. Klaassen that 800 ppm would have been an appropriate exposure concentration in the 2-year rat studies based on survival in the 13-week studies. Dr. Karol said if gross and histopathological changes observed in rats exposed to 800 ppm were part of the rationale for choosing 400 ppm as the highest exposure concentration for the 2-year studies, a statement should be added. Dr. Bucher disagreed and explained that when setting exposure concentrations based on lethality, the aim is to set the highest exposure concentration slightly greater than a quarter of the lethal dose determined in the 13-week studies unless there is good evidence for a pharmacologic action that is the cause of death. Dr. Karol further commented on the "uncertain" association between acetonitrile exposure and liver neoplasms in male rats that appeared to be based on historical control data showing a 10% incidence of liver neoplasms in feed studies. She said that concurrent controls and the historical data from inhalation studies would be more relevant and likely would support a causal relationship. Dr. Bucher acknowledged that an argument could be made for *some evidence*, but based on the lack of a strong dose-related response, no increase in preneoplastic lesions or atypical foci, and up to four neoplasms in the control groups in some inhalation studies, *equivocal evidence* was considered to be the best conclusion.

Dr. Taylor moved that the Technical Report on acetonitrile be accepted with the revisions discussed and with the conclusions as written for male rats, *equivocal evidence of carcinogenic activity*, and for female rats and male and female mice, *no evidence of carcinogenic activity*. Dr. Klaassen seconded the motion, which was accepted unanimously with 11 votes.